Remarks

Claims 54-123 are pending in the application, with claims 54, 68, 78, 92 and 107 being the independent claims. Claims 54, 68, 78, 92 and 107 have been amended. Support for the claim amendments may be found in the original claims and throughout the specification. See, for example, Example 1 and the Sequence Listing (filed April 5, 2004). Thus, no new matter is added by way of these amendments, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 54-123 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Huo (U.S. Patent No. 5,922,535) in view of Chenchik (U.S. Patent No. 5,962,271). Applicants respectfully traverse this rejection.

Establishing *prima facie* obviousness requires a showing that some combination of objective teachings in the prior art and/or knowledge available to one of skill in the art would have lead that individual to arrive at the claimed invention. *See* In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Proper consideration of the prior art requires that the PTO not pick and choose to apply only those portions of the prior art which support the proposition that the applicants' claimed invention is unpatentable. *Id.* at 1075. This is impermissible hindsight. The Supreme Court has recently warned "of the distortion caused by hindsight

bias" and cautioned against "arguments reliant upon *ex post* reasoning." *See* KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1742 (2007).

In order to avoid hindsight bias, it is particularly important that the teachings of prior art references must be considered in their entirety, *i.e.* as a whole, including those parts that teach away from the claimed invention. *See* W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). The Federal circuit has stated that "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by applicant." *See* In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). The Supreme Court also recently indicated that teaching away from a claimed invention is a likely indicator that the invention is not obvious: "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *See* KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007). Thus, an "applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *See* In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997).

The present claims are drawn to methods of making one or more cDNA molecules involving at least one primer adapter nucleic acid molecule comprising one or more ligands and one or more cleavage sites. More specifically, the claimed methods involve a cleavage step, whereby the cleaved cDNA molecules are released from the hapten-cDNA molecule

complexes or solid support-cDNA molecule complexes and whereby the cleaved cDNA molecules do not comprise the ligand portion of the primer-adapter nucleic acid molecule.

Huo teaches standard cDNA synthesis from mRNA using biotinylated primers in cDNA synthesis to facilitate attachment of synthesized cDNA to solid supports. *See* Huo at column 12, lines 9-24. Huo further teaches using biotinylated primers comprising rare restriction sites at their 5' ends and subsequent cleavage by a restriction enzyme to create overhangs that are filled in with biotinylated nucleotides. *Id.* at column 13, lines 40-52.

Chenchik teaches cDNA synthesis using primers that comprise rare restriction sites to facilitate cloning of cDNAs into cloning vectors. *See* Chenchik at column 9, lines 17-25).

Skilled artisans, considering the cited references as a whole, would not have combined the noted teachings to achieve the claimed invention. This is at least because the Huo reference specifically teaches away from the claimed methods. Huo teaches biotinylated primers that are "preferably biotinylated either in the restriction recognition sequence or at the poly-T portion" and that "the primer[s] should be biotinylated in such a way that biotinylation does not interfere with restriction digestion, ***and that at least one biotinylated nucleotide is retained on the primer after cleavage (i.e. at least one labeled nucleotide is located 3' of the cleavage site).***" *See* Huo at column 13, lines 20-26 (emphasis added). In other words, Huo's methods involve biotinylated primers that are specifically designed so that cDNA molecules will comprise at least one ligand (*i.e.*, biotinylated nucleotide) after cleavage. This is in direct contrast to the present methods which claim that the cleaved cDNA molecule "***does <u>not</u> comprise the ligand portion" or "biotin moiety portion of the primer-adapter nucleic acid molecule.***" Thus, combining the

Huo reference, considered in its "entirety," with the Chenchik reference would have lead skilled artisans at the time the application was filed in a direction divergent from the path that was taken by the Applicants – in a way that would not have lead a skilled artisan to combine the cited references in such a manner as to arrive at the claimed invention.

As is the case here, "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *See* KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007). Thus, *prima facie* obviousness has not been established and Applicants therefore respectfully request that the rejection of claims 54-123 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

Date: January 22, 2008

/Bernadette M. Perfect/
Reg. No. 53,267
Bernadette M. Perfect
Agent for Applicants

Invitrogen Corporation
1600 Faraday Ave.
Carlsbad, CA 92008
(760) 476-7120